In the Drawings:

Please replace originally filed Figures 4, 10, 14 and 15 with substitute Figures 4, 10, 14 and 15. A Request for Draftsperson's Approval of Drawing Change, with marked up original Figures 4, 10, 14 and 15 and substitute Figures 4, 10, 14 and 15 is attached hereto.

Remarks

The Claims

Claims 1, 18-19, 21-22, and 37-39 have been canceled without prejudice and claims 42-94 will be pending upon entry of this amendment. Support for amended claims 55 and 89 is found, for example, at page 4, lines 1-12; at page 17, lines 11-15; at page 21, line 24 through page 22, line 4 (in particular, line 30); at page 25, lines 23-36; and in Figures 1A-C.

No new matter has been added by way of amendment.

The Drawings

Figures 4, 10, 14, and 15 have been amended according to the Examiner's instructions (rejection of claims 42-112 under 35 U.S.C. § 112, second paragraph). The drawings have been amended to delete any reference to the term "VEGI" and replace therefor with the inhouse synonymous term -- TNF-gamma --. As required by 37 C.F.R. § 1.121(a)(3), substitute sheets of the revised drawings and copies of the original drawings showing the proposed changes in permanent red ink are submitted herewith. No new matter has been introduced.

No new matter has been added by way of amendment.

Rejections of the Claims

I. Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 42(d), 42(h), and 49-94 under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. In particular, the Examiner contends that:

> while being enabling for the full length nucleic acids and the encoded protein therefrom, does not reasonably provide enablement for: 1) any fragment that may have TNF-γ alpha activity . . . ; 2) nor is there enablement for any 30 contiguous nucleic acids that will encode for about any 10 contiguous amino acid sequence . . . , or any 30 contiguous amino acids . . . ; 3) there is lack of enablement for any fragment that binds an antibody to TNF-γ alpha . . . ; 4) to heterologous sequence or heterologous sequence that encodes for any polypeptide that is linked to the claimed nucleic acid sequence . . . .

See, Paper No. 8, Paragraph 4. The Examiner further alleges that:

> [t]he skilled artisan would be faced with an undue amount of experimentation for determining how long the encoded fragment must be; from what region/portion on the encoded protein the fragment covers, represents or corresponds to; does the encoded fragment have to represent a contiguous string of amino acid residues on the encoded protein's structure; because knowledge of these variables with assurances that the encoded fragment is biologically active for regulating endothelial cell growth must be provided in order to satisfy the requirement for enablement.

See id.

Applicants respectfully disagree and traverse.

Preliminarily, Applicants point out that in order to enable the claimed invention as required by 35 U.S.C. § 112, the specification need only enable a person of ordinary

skill in the art to make the claimed nucleic acids and practice *a single* use of the claimed nucleic acids without undue experimentation.[1] Thus, Applicants submit that to be fully enabled, the polypeptides of the invention do not necessarily have to exhibit a biological activity, but need merely have application in a single use, such as, for example, as a polypeptide that binds an antibody to a TNF-gamma-alpha polypeptide.

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 USPQ 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

Furthermore, "[t]here is no magical relation between the number of representative examples and the breadth of the claims" with respect to enablement. *In re Borkowski*, 164 USPQ 642, 646 (C.C.P.A. 1970). The issue is not whether the specification discloses any or all alterations that can be made in the claimed polypeptides that will not alter their functional activity, but rather whether polypeptides encompassed by the claims have at least a single use, and this use can be confirmed, without undue experimentation, by following procedures either described

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[1] The Applicant need show utility for only one disclosed purpose. See, *Raytheon Co. v. Roper Corp.*, 220 USPQ 592 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984); *Ex parte Lanham*, 121 USPQ 223 (Pat. Off. Bd. App. 1958).

in the specification or otherwise known in the art. *See, In re Angstadt*, 190 USPQ 214, 218 (C.C.P.A. 1976):

> To require such a complete disclosure would apparently necessitate a patent with "thousands of examples . . . More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments . . . .

While the predictability of the *art* can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the *result* of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is *not* a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 USPQ 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original). As Judge Rich explained in *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed.Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to *determine*, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility" (emphasis provided). Since the disclosed or otherwise known methods of making and screening polypeptides (including fragments and variants) may be used to make and then *determine*, without undue experimentation, whether a given polypeptide encompassed by the claims is able to function as a

polypeptide that binds an antibody to TNF-gamma-alpha, and therefore possesses the disclosed utility, the enablement requirement is fully satisfied. *In re Wands*, 8 USPQ2d at 1404; *Ex parte Mark*, 12 USPQ2d 1904, 1906-1907 (B.P.A.I. 1989).

Applicants submit that the specification provides ample guidance for one of ordinary skill in the art to routinely make and use the claimed polypeptides. In particular, the specification discloses the molecular characterization of the TNF-gamma-alpha polypeptides (including fragments and variants). Figure 17 of the specification, discloses the antigenic index of the TNF-gamma-alpha polypeptides predicted using the Jameson-Wolf computer algorithm, predicting that eight specific regions of this protein will be antigenic. *See, e.g.*, specification, at page 25, lines 1-22. The specification further teaches methods for generating antibodies to the TNF-gamma-alpha polypeptides of the invention. *See, e.g.*, specification, at page 73, line 23 through page 74, line 2; and at page 74, line 17 through page 79, line 22. Antibodies generated according to the methods disclosed in the specification may routinely be applied to determine whether the TNF-gamma-alpha polypeptides (including fragments and variants) bind an antibody to the TNF-gamma-alpha polypeptide disclosed in Figures 1A, 1B, and 1C. The specification also teaches that antibodies generated against the TNF-gamma-alpha polypeptides of the invention have diagnostic and therapeutic applications. *See, e.g.*, specification, at page 85, line 14 through page 86, line 11; and at page 87, line 31 through page 88, line 6. In addition, contrary to the Examiner's contention, the specification teaches a number of assays that may be routinely applied to measure the ability of TNF-gamma-alpha polypeptides and fragments thereof to elicit TNF-gamma-alpha related biological activities. *See, e.g.*, specification, at page 74, lines 7-12, and Examples 5, 6, and 9-15.

In fact, contrary to the Examiner's contention that the specification ". . . does not reasonably provide enablement for: 1) any fragment that may regulate endothelial cell growth . . . ," the specification as originally filed teaches specific activities of several TNF-gamma-alpha polypeptide deletion mutations of that regulate endothelial cell growth. For example, Example 9 of the specification teaches an *in vitro* angiogenesis assay and provides data that demonstrate that a polypeptide expressed from a construct encoding amino acid residues 12-147 of the TNF-gamma-alpha polypeptide shown as SEQ ID NO:2 to inhibit the FGF-2-induced formation of capillary-like tubular structures in cultures of adult bovine aortic endothelial (ABAE) cells.

Given the foregoing teachings of the specification, it cannot be said that the invention as claimed is not enabled. Moreover, Applicants submit that the skilled protein chemist, molecular biologist, or immunologist, enlightened by the teaching of the present specification is more than capable of routinely generating the claimed polypeptides and determining whether a polypeptide encompassed by the claims functions as a polypeptide that binds an antibody to the TNF-gamma-alpha polypeptide.

Applicants disagree with Examiner's allegations that the specification provides no guidance for the specific regions of the encoded protein that could tolerate changes and submit that the specification fully enables the claimed polypeptides. Applicants point out that, as discussed above, the enablement requirement of 35 U.S.C. § 112 is fully satisfied if the specification enables a person skilled in the art to make the claimed polypeptides and practice *a single* use of the claimed polypeptides, such as, for example, use of the polypeptides to generate antibodies that specifically bind TNF-

gamma-alpha, without undue experimentation. As discussed above, the antigenic index presented on Figure 17 of the specification disclose specific regions of TNF-gamma-alpha predicted to be antigenic. The design of polypeptides having 30 contiguous amino acid residues of a known reference polypeptide sequence of 174 amino acids is routine in the art. Accordingly, Applicants submit that one skilled in the art, enlightened by the disclosure and guidance of the instant application, is more than capable of making and using TNF-gamma-alpha polypeptides having at least 30 contiguous amino acids.

Moreover, Applicants respectfully submit that heterologous sequences fused to the TNF-gamma-alpha polypeptides of the invention are also fully enabled by the specification as originally filed. Heterologous sequences are taught throughout the specification and were well known by one of ordinary skill in the art at the time the present application was filed. The specification clearly teaches fusion of the polynucleotides and/or polypeptides of the invention to, for example, recombinant vectors, leader sequences, purification tags, stabilization polypeptides, as well as immunoglobulin polypeptides, dimerization domains, cell surface display polypeptides, enzymatic polypeptides, fluorescent polypeptides, luminescent polypeptides, and many others. *See, e.g.*, specification, at page 6, lines 10-14; at page 19, lines 3-23; at page 33, line 33 through page 41, line 14; and at page 70, line 36 through page 71, line 32. Based on the disclosure of the present specification and the knowledge of one of ordinary skill in the art at the time the application was filed, it is clear that one of ordinary skill in the art would have been able to make and use the invention commensurate with the scope of the claims.

Applicants submit that because of (1) the disclosure and characterization in the specification of the polypeptide sequence corresponding to TNF-gamma-alpha and fragments thereof; (2) the availability of routine techniques for generating fragments or variants to a known polypeptide sequence, for expressing the polypeptide fragments or variants, and for generating antibodies against the polypeptide; and for assaying the ability of an antibody to bind a polypeptide; (3) the high level of skill in the field of molecular biology and immunology; and (4) the direction and guidance provided by the specification, one skilled in the art could routinely generate the claimed polypeptides and determine whether these polypeptides bind an antibody to the TNF-gamma-alpha polypeptide.

In view of the foregoing, Applicants submit that the claims fully meet the enablement requirements of 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection be withdrawn.

II. Rejections Under 35 U.S.C. § 112, Second Paragraph

A. SEQ ID NOs

The Examiner has rejected claims 42-94 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. In particular, the Examiner alleges that "[w]hile all of the elected claims appear to be directed to the alpha (α) form of TNF-gamma (γ), it is not exactly clear from the specification which Seq Id is the alpha or beta form of TNF-γ." *See*, Paper No. 8, Paragraph 4. More in particular, the Examiner contends that at page 6, at the bottom of page 8, and "at several [other] pages in the specification," Applicants indicate that

SEQ ID NOs:19 and 20 and ATCC Deposit No. 203055 correspond to TNF-gamma-alpha molecules of the invention rather than TNF-gamma-beta molecules of the invention.

Applicants have amended the specification as indicated above to correct typographical errors regarding the identity of the TNF-gamma-alpha and TNF-gamma-beta sequences and ATCC deposits associated with the invention. Applicants affirmatively state the following information regarding the TNF-gamma-alpha and TNF-gamma-beta molecules of the present application:

Molecule of the Invention	***Corresponding SEQ ID NOs.***	***Corresponding ATCC Deposit Nos.***
TNF-gamma-alpha	1, 2	75927
TNF-gamma-beta	19, 20	203055

Support for the information as supplied in the above table is found throughout the specification as originally filed. *See, for example*, specification, at page 4, lines 1-22; at page 16, lines 19-25; and in Figures 18A-D, 19, and 20A-B. Applicants affirm that each reference to either TNF-gamma-alpha and/or TNF-gamma-beta throughout the specification should reflect the information in the table above. Applicants have amended the specification accordingly, and therefore respectfully request that the rejection of claims 42-94 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

B. TNF-Gamma-Alpha

The Examiner has rejected claims 42-94 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and

distinctly claim the subject matter that Applicants regard as the invention. In particular, the Examiner contends that:

> [t]he specification also renders the claims confusing or contradictory in referring to the protein as TNF-γ-α, but several of the figures use VEGI. There should be consistency in the terms used to identify and claim applicants' product. Further, based on the statements in the specification, when the figures use VEGI, it is not sure if this refers to the alpha or beta form of TNF-γ.

See, Paper No. 8, Paragraph 4.

Applicants submit herewith amended drawings for the present application. The term "VEGI" no longer appears in any of the drawings. The term "VEGI" is an inhouse synonym for TNF-gamma. In view of the absence of the term "VEGI" in the amended drawings, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 42-94 under 35 U.S.C. § 112, second paragraph.

C. Markush Groups

The Examiner has rejected claims 75-88 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. In particular, the Examiner contends that the rejected claims are "indefinite and confusing in the manner in which the claims is [sic] drafted, because it is not clear if the alternative embodiments of the Markush group defines the first polynucleotide or the second nucleotide [sic]."

Although Applicants respectfully disagree, claim 75 has been amended to specifically indicate whether the first or second amino acid sequences are intended to be recited. The remaining claims either already recite the terms "first" or "second" or

depend from claim 75. Thus, Applicants respectfully submit that the rejection of claims 75-88 has been obviated, and therefore respectfully request that it be reconsidered and withdrawn.

III. Rejections Under 35 U.S.C. § 102(a) or, in the Alternative, Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 55-94 under 35 U.S.C. § 102(a) as allegedly anticipated by, or, in the alternative, under 35 U.S.C. § 103(a) as allegedly obvious over Burns et al., Lowe, or Culler et al In particular, the Examiner contends that:

> [a]ccording to the sequence alignments between the [alleged] prior art and claimed nucleic acids [sic], there is sufficient identity that would allow the claimed nucleic acids [sic] to hybridize to the [alleged] prior art sequences, or they also satisfy the claim limitation of being at least 30 nucleotides. Thus, the instant claims are anticipated by the [alleged] prior art or at least rendered prima facie obvious therefrom, and the burden is upon applicants to establish a patentable difference . . . .

See, Paper No. 8, Paragraph 5.

Applicants respectfully disagree. However, solely in the interest of facilitating prosecution, and not in acquiescence to the Examiner's allegations, Applicants have amended claims 55 and 89 to refer only to that portion corresponding to the open reading frame in SEQ ID NO:1 and the cDNA that was deposited as ATCC Deposit No. 75927. Claims 65 and 75 are unaffected by the references cited by the Examiner. These claims refer to SEQ ID NO:2 or the polypeptide encoded by the cDNA deposited as ATCC Deposit No. 75927. The polynucleotides disclosed in the references cited by the Examiner partially align with SEQ ID NO:1 of the invention well outside of the open reading frame taught by the specification as SEQ ID NO:2.

Because the references cited by the Examiner align with SEQ ID NO:1 outside of the open reading frame as disclosed in the present specification, they neither anticipate nor render obvious the claimed invention. For this reason, the references cited by the Examiner (*i.e.*, Burns, et al., Lowe, and Culler, et al.) are not available for use under 35 U.S.C. §§ 102 and 103 in any way. Accordingly, Applicants respectfully submit that the rejection of claims 55-94 under 35 U.S.C. § 102, or in the alternative, under 35 U.S.C. § 103(a), has been obviated. Applicants therefore respectfully request that the rejection be reconsidered and withdrawn.

Conclusion

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the instant application. Applicants believe that this application is in condition for substantive examination. If in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below.

If there are any fees due in connection with the filing of this paper, please charge the fees to Deposit Account No. 08-3425.

Respectfully submitted,

Date: January 16, 2001

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Enclosures
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